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DISTINGUISHING BETWEEN HALOPERIDOL'S AND DECAMETHONIUM'S DISRUPTIVE EFFECTS ON OPERANT BEHAVIOR IN RATS: USE OF MEASUREMENTS THAT COMPLEMENT RESPONSE RATE

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The behavioral effects of haloperidol (0.04 to 0.16 mg/kg) and nonparalytic doses of decamethonium (0.2 to 0.8 mg/kg) were studied with operant methods that permitted the measurement of response rate, peak force of response, duration of response, and duration of the rat's head entry into the reinforcement dipper well. Type of operant response topography (forelimb press or forelimb grasp-and-pull) and peak force (low or high) required for reinforcement delivery were independent variables. The low-force, press-topography condition yielded qualitatively different profiles for the two drugs. Haloperidol increased peak force and duration of operant response, increased maximum head entry duration, and temporally dissociated forelimb and head entry behavior. Decamethonium decreased force and duration of operant response, did not appreciably affect maximum head entry duration, and did not influence the normal temporal coupling of forelimb and head entry responses. The haloperidol effects were seen as reflections of pseudo-Parkinsonism, not muscle weakness, which appeared to be the primary source of decamethonium's behavioral effects.

Key words: haloperidol, decamethonium, response force, response duration, dopamine, neuroleptic, pseudo-Parkinsonism, rat

The central purpose of this paper is to contrast the behavioral effects produced by the neuroleptic, haloperidol, with the effects engendered by the paralytic agent, decamethonium bromide (hereafter referred to as decamethonium). In other words, are the operant behavioral effects of haloperidol similar to, or different from, the peripherally induced muscle weakness caused by decamethonium? Such a comparison was made as part of a continuing effort to understand the pharmacological effects through which neuroleptics influence the operant behavior of rats. In this context, decamethonium was selected as an agent to produce peripherally mediated musculoskeletal weakness (Fantie & Nakajima, 1987; Zaimis, 1953), and haloperidol was selected as the prototypical high-potency D2 dopamine receptor blocker (Hyttel, Larsen, Christensen, & Arnt, 1985). In the human clinical setting, haloperidol and other high-potency neuroleptics produce acute motoric side effects known as acute dystonia and pseudo-Parkinsonism (for a recent review see Tarsy, 1989). Whether or not the well-documented operant rate decrements produced by neuroleptics in rodents (e.g., Fowler, 1990; Sanger & Blackman, 1987; Wise, 1982) can validly be taken as manifestations of motor effects similar to those found in humans remains unresolved. Lack of agreement in the literature on this issue is derived, in part, from two broad procedural deficiencies of past work: Investigators have used a relatively narrow range of behavior-controlling conditions for examining operant effects of neuroleptics, or they have relied on response rate as the single measure of the effects of neuroleptics.

Many behavior-controlling conditions can influence response rate; in the absence of a careful experimental analysis of the effects of such independent variables, it is hazardous to speculate on the antecedents of a particular pattern of rate decrement. Accordingly, the work reported here examined the possible influence of two independent variables that may affect behavioral output under the influence of haloperidol. These variables were response topography and force of response required for reinforcement. Both were chosen on the basis

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of their a priori relationship with the motoric demands of responding.

The current work addressed the problem of relying exclusively on response rate as an outcome variable in two ways. First, just as a better understanding of an observed drug-induced rate change can be obtained by experimentation with different behavior-controlling independent variables, greater insight may be gained by expanding the range of dependent variables used to characterize the behavior (Fowler, 1987). Consequently, peak force and duration of individual operant responses were used to complement the rate variable and to provide important new information pertinent to defining the low-dose motor effects of neuroleptics in rats. Second, measurement of adjunctive behavior (derived from the rat's insertion of its head into the reinforcement dipper well) broadened even further the dependent variables used to characterize the differences between haloperidol and decamethonium.

Availability of multiple dependent variables afforded the opportunity to compare, in terms of peak force and duration of response, the two drugs at doses that were approximately equally effective in suppressing response rate. This was important because response rate itself can be a determinant of a drug's effects (e.g., Dews, 1981), and qualitative comparisons between two drugs become more meaningful if response rate per se can be ruled out as the source of observed differences. This approach is analogous to the research tactic of arranging equal rate performances as a precondition for comparing the effects of a single drug on behavior maintained by two different events (e.g., Barrett & Katz, 1981).

METHOD

Subjects

Sixty-four male Sprague-Dawley rats from the Holtzman Co. served as subjects. Half of the rats received haloperidol; these were received in early May 1989 and were used in the described procedures through July 1989. The other half, which received decamethonium bromide, resided in the laboratory from late September through mid-December 1989. The use of water reinforcement dictated restricted access to water for all subjects. An interval of 30 min to 1 hr separated the end of conditioning sessions and a daily period of 4-min access to water. This procedure permitted slow weight gain during the course of the behavioral observations: For the haloperidol rats, mean body weight on the 1st day of continuous reinforcement (CRF) training was 379.0 g (standard deviation [*SD*] = 27.6 g), with the mean body weight reaching 423.6 g (*SD* = 30.4 g) on the last day of drug treatment. Mean body weights for the rats receiving decamethonium were 356.8 g (*SD* = 39.4 g) on the 1st day of CRF training and 410.7 g (*SD* = 41.6 g) on the final day of drug treatment. Throughout their stay in the laboratory, the rats received free access to Purina® rat chow in their individual home cages.

Apparatus

Eight operant conditioning/recording chambers were used. Each chamber was fitted with a solenoid-activated reinforcement dipper. The force-sensing operanda were located outside the operant chamber and were accessible through a rectangular aperture (2 cm high and 3 cm wide, with the lower edge of the opening 6 cm above the floor). The portion of the operandum nearest the rats was 2.5 cm from the inside wall of the chamber. Positioning the operanda outside the chambers ensured uniform response topographies by limiting operandum contacts to the forelimbs (i.e., it was not possible for the subject to register force by using the snout or teeth). The chambers were located in separate sound-attenuating plywood enclosures equipped with squirrel cage exhaust fans. The important details of operant force measurement techniques have been published elsewhere (Fowler, 1987), as have the dimensions of the chambers and the spatial specifications of operandum positioning (Fowler, Gramling, & Liao, 1986). Details differing from the published accounts were as follows: The force transducers were SensoTec® Model 31, Zenith 159 computers (one computer per two chambers) collected the measurements and programmed the contingencies, and interfacing consisted of four LabTenders® and digital buffering and power drive circuitry from life Science Associates. The transducer electronics passed frequencies below a 100-Hz cutoff. This is a most important detail because previous work (Ford, Fowler, & Nail, 1979; Fowler, 1987) using a 10-Hz high-frequency cutoff often did not reliably detect peak force effects that are easily seen when the 100-Hz cutoff

is used. Half of the chambers made use of a horizontal discoidal operandum (18 mm in diameter), and the other four chambers had operanda constructed from stainless steel wire (1 mm diameter) that provided an 18-mm "grasping bail" for the rat to grab with its flexed forepaw digits. Not heretofore published are the details of the photobeam detector positioned in each chamber that was used to record the duration of the rat's insertion of its head (head entry) into the dipper well. The photodetector was based on a modification of the circuit described by Batson and Turner (1986), but with no lens beyond that provided by the infrared light-emitting diode (LED). The LED–detector pair was located in a cylindrical PVC collar (2.5 cm long with a 5.8-cm inside diameter). The collar mated with the Gerbrands stainless steel dipper well (5.5 cm in diameter and 2.7 cm deep, with a 1.25-cm hole giving access to the dipper); the shaft of the photobeam was parallel to, and 2.0 cm above, the plane of the chamber floor and was 1.0 cm outside the plane of the chamber's front panel. In essence, the PVC collar and dipper well together formed a "tunnel" (5.2 cm long) into which the rat inserted its head in order to lick from the presented dipper.

Procedure

A 2 × 2 completely randomized factorial design (two levels of response topography and two levels of required force with independent groups in each of the four cells) was carried out once for haloperidol, and was then repeated at a later time with new subjects that received decamethonium. The two types or response topography were "press" and "pull." To execute a press response, the rat had to extend its forelimb and make a downward vertical strike on the disk-shaped operandum. For the press, the peak force requirement for reinforcement delivery was 8 g in the low-force condition and 32 g in the high-force condition. For both low- and high-force conditions, reinforcement was delivered upon removal of the forepaw from the operandum. All responses of 8 g or above were recorded in both groups; thus, the force level used for defining the response was the same for both press groups, but the forces required for reinforcement delivery were different. A similar procedure was used for the pull topography, except that the low-force requirement (for reinforcement) was 8 g and the high-force requirement was 96 g. The high-force requirement differed for the two topographies because previous work indicated that a 32-g press requirement generated about the same proportion of subcriterion responses as did the 96-g pull requirement (Fowler, Gramling, & Liao, 1986). The low-force requirement of 8 g for both topographies was selected because this value presents a negligible requirement in that spontaneous force emissions during shaping easily met or exceeded 8 g. The threshold for defining a response was not set any lower in order to avoid recording as responses any artifact due to vibrations arising from the dipper solenoid or from lack of complete electronic filtration of natural frequency oscillations. (See the caption of Figure 1 for abbreviations used to represent the required force and topography conditions.)

The training procedures used to produce the final behavioral baseline were (a) magazine approach training, (b) manual shaping of required response topographies, (c) additional upward shaping of peak force of response in the treatment groups exposed to the high-force requirements, and (d) CRF training. With the exception of some of the manual shaping sessions (whose durations were dictated by a joint function of the subjects' behavior and the trainers' judgment), all sessions were 15 min in length.

Magazine training, lasting two sessions, was directed by a computer program that presented the 0.1-mL dipper for 5.0 s contingent upon a head entry event as detected by photobeam interruption. During this phase, the aperture allowing access to the operandum was covered. In all subsequent phases, dipper access time was 3.0 s, and the operandum aperture was uncovered.

Shaping the required response was carried out by the method of successive approximations. The method was augmented by beginning the shaping process with the operandum almost touching (i.e., 0.5 mm) the chamber outside wall. As shaping progressed, the operandum was gradually withdrawn to its final position 2.5 cm beyond the chamber wall. With the operandum at this distance only forelimb responses were possible. A rat was considered to have acquired adequately the designated response when it had obtained 50 unassisted reinforcers at an 8-g criterion for reinforcement with the operandum in its final position. The

trainers worked with a few rats daily for 1 month until all rats had met the acquisition criteria; four to six shaping sessions were required for each rat. In equal steps over the next four sessions, for the high-force rats, the criterion force was raised from 8 g to the final criterion value (either 32 g or 96 g, depending on type of topography). Then CRF training was carried out for 24 days in the haloperidol experiment and for 14 days in the decamethonium experiment. The larger number of CRF sessions in the haloperidol groups was the result of personnel problems that caused multiday gaps in conducting the experiment, thereby dictating extra training days to ensure four consecutive sessions before drug treatment commenced. Across these four sessions, the mean number of head entries differed from the grand mean for these days by less than ±6% for each experiment. Number of head entries was thought to mirror the number of reinforcers earned and thus to reflect conformity of the behavior to the contingencies. Although number of head entries appeared a priori to be a reasonable criterion measure of stability of responding, the analysis of the peak force results indicated that it would have been useful to monitor mean peak force daily and to use it as an additional variable to characterize stability. With the computer and personnel resources available at the time of data collection, it was not possible to do this.

Drugs. Drug solutions were injected intraperitoneally in a volume of 1 mL/kg. For both drugs, the dose was counterbalanced across order of administration. Each drug evaluation session was preceded by a vehicle session and followed by a no-injection session. With this procedure, drug injections were separated by 72 hr. Haloperidol (0.04, 0.08, 0.12, 0.16 mg/kg, free base) was dissolved in a mixture of physiological saline and sufficient lactic acid and to achieve solution. Decamethonium bromide (0.2, 0.4, 0.8 mg/kg, expressed as the salt) was dissolved in physiological saline. Haloperidol was injected 45 min before testing, and decamethonium was injected 15 min before testing.

One of the premises of this work is that dependent variables other than response rate may play a useful role in describing the behavioral effects of drugs. Accordingly, multiple dependent variables were used to characterize both the operant itself and adjunctive behavior comprising portions of the operant–reinforcer–consumption–operant cycle of behavior. The operant forelimb measures were average response rate (number of responses divided by session time), mean peak force (the mean of the distribution of the peak forces for the responses emitted by 1 subject in one session), mean response duration (the mean of the rat's response duration distribution of separate responses made in a single session), and interresponse time (IRT). Response rate of forelimb responses was based on all recorded responses (both criterion responses and subcriterion responses). Subcriterion responses for the high-force groups were included in the rate measure to avoid confounding the definition of a response with the force required for reinforcement. In the case of such confounding, one can never determine whether the rate measure under high-force conditions is influenced by changing the definition of response or by changing the force required for reinforcement. Or, put differently, rate of response of the high- and low-force groups is not a proper comparison if the physical definition of a response is different in the two conditions.

The adjunctive measures were average rate of head entry events (number of dipper well head entries divided by session time), maximum head entry duration (the maximum value of the distribution of separate head entries for a given rat and session), and interentry intervals (IEI, analogous to IRT).

The between-groups experimental design used here departed from the traditional operant behavioral pharmacology approach because of the possibility of pronounced pharmacological and behavioral carryover effects. Such carryover effects make the reestablishment of comparable baselines for individual subjects problematic, especially when one is recording several dependent variables (e.g., although response rate may return to baseline, response force or duration may not, depending on the treatment). With respect to pharmacological effects, it is well established that multiple dosing with haloperidol and other neuroleptics can have large cumulative effects that appear to be unrelated to drug accumulation per se (Wise, 1982). Unpublished data from our laboratory indicate that such repeated dosing effects with haloperidol occur even in the face of highly stable response rates on days between the haloperidol treatments. With re-

spect to behavioral carryover effects, our experience suggests that the effects of training a rat to perform a specific operant topography can endure for a long time despite massive training on a new topography (such as switching from a pull to a press). These transfer effects have received little formal attention. In view of the dearth of information on this question, we decided that it would be better to eliminate transfer effects by experimental design because the option of performing the behavioral studies necessary for understanding such effects would have been prohibitively expensive.

RESULTS

Data for response rate, mean peak force, mean duration, head entry rate, and maximum head entry duration were analyzed with conventional group-based statistical methods and with additional methods that highlight the importance of examining the effects of drugs on the behavior of individual subjects. Analysis of variance (ANOVA) techniques were seen as a convenient means of describing the interaction of dose effects with response topography and/or required force of response. Additional analyses, not derived from hypothesis-testing statistical models, illustrated the shortcomings of relying on ANOVA alone, and, more importantly, provided a successful strategy for disclosing qualitative differences between haloperidol and decamethonium at approximately equipotent doses for reducing response rate.

Group Data

Response rate. As shown in Figure 1 (and supported statistically in Table 1), in neither the haloperidol-treated rats nor the decamethonium-treated rats were significant topography (press vs. pull) effects observed for response rate. However, in the haloperidol-treated rats, topography interacted significantly with required force in affecting response rate. This ANOVA result confirmed the graphic separation (Figure 1, upper left) of the pull-high rats from the other three groups. A similar trend was seen for the rats receiving decamethonium (Figure 1, upper right), but it was not significant. This difference in ANOVA results between haloperidol and decamethonium is probably not related to the potency or other differences between the drugs, but is rather related to the different amounts of training and attendant precision of force differentiation attained at the time drug treatment commenced. It should be recalled that, for purposes of calculating response rate, responses were defined in terms of 8 g of force, but criterion responses were defined in terms of the force requirement (i.e., the operations for counting responses were the same for all groups regardless of the force requirement for reinforcement). Thus, the tendency for higher rates to occur in the high-force groups is a reflection of the fact that rats always make subcriterion responses, and relatively large numbers of subcriterion responses are made when the force requirements are challengingly high (see Notterman & Mintz, 1965, and Fowler, 1987, for a discussion of these issues).

Both haloperidol and decamethonium had substantial response rate-reducing effects that varied with dose (Table 1 and Figure 1, top row). Over the dose ranges used, haloperidol's effects were more graded than those of decamethonium. The significant interaction of dose with required force in the decamethonium-treated rats suggests that the pull-high group exhibited a more precipitous decline in rate at the 0.80 mg/kg dose than did the other groups.

Forelimb mean peak force. Both topography and required force had large effects on mean peak force of emitted responses (Figure 1, middle row). The higher forces in the high-force conditions (press-high and pull-high) are an indication that the rats adjusted their force emission to reflect the force-based reinforcement contingency. The differences in force emission produced by response topography are not so easily understood because the pull-low groups continued to emit forces much higher than the 8-g requirement even though there was no necessity for excess force. The rats' relatively poor force differentiation with the pull topography is consistent with other reports (Fowler, Lewis, Gramling, & Nail, 1983; Kirkpatrick & Fowler, 1989), and may be related to unconditioned elicited components of response emission that interfere with force differentiation (Kirkpatrick & Fowler, 1989).

Consistent with previous reports (Fowler & Kirkpatrick, 1989; Fowler, LaCerra, & Ettenberg, 1986), haloperidol had a small but significant force-elevating effect as indicated by ANOVA (see Table 1). The significant dose

Table 1

Analysis of variance statistics for the data shown in Figures 1 and 2. Statistics are listed only where conventionally significant probability values were obtained; the three-way interaction results are not listed because none were significant. Forelimb refers to the operant response, either a press or a pull, measured with a force transducer. The head entry data were recorded for the same rats by a photobeam detector located at the entrance to the reinforcement dipper well. Mean peak force and duration of the operant and maximum head entry duration were log transformed before the calculations were performed.

		Haloperidol			Decamethonium		
Dependent variable	Type of effect[a]	*df*	*F*	*p*	*df*	*F*	*p*
Forelimb response rate	T	—	—	—	—	—	—
	RF	1, 28	10.73	.003	—	—	—
	T × RF	1, 28	11.10	.002	—	—	—
	D	4, 112	38.86	.001	3, 84	33.15	.001
	D × T	—	—	—	—	—	—
	D × RF	—	—	—	3, 84	4.59	.005
Forelimb mean peak force	T	1, 28	63.26	.001	1, 23	126.27	.001
	RF	1, 28	25.19	.001	1, 23	19.66	.001
	T × RF	—	—	—	—	—	—
	D	4, 112	4.05	.004	—	—	—
	D × T	—	—	—	—	—	—
	D × RF	4, 112	3.71	.007	—	—	—
Forelimb mean duration	T	—	—	—	1, 23	12.17	.002
	RF	1, 28	15.37	.001	1, 23	14.12	.001
	T × RF	—	—	—	—	—	—
	D	4, 112	10.72	.001	—	—	—
	D × T	4, 112	5.57	.001	3, 69	5.51	.002
	D × RF	4, 112	3.45	.011	—	—	—
Head entry rate	T	—	—	—	—	—	—
	RF	—	—	—	—	—	—
	T × RF	—	—	—	—	—	—
	D	4, 112	49.61	.001	3, 75	45.51	.001
	D × T	—	—	—	—	—	—
	D × RF	—	—	—	—	—	—
Head entry maximum duration	T	—	—	—	—	—	—
	RF	—	—	—	—	—	—
	T × RF	—	—	—	—	—	—
	D	4, 112	29.81	.001	—	—	—
	D × T	—	—	—	—	—	—
	D × RF	—	—	—	—	—	—

[a] T = topography, RF = required force, D = dose.

× required force interaction further suggested that haloperidol's effects on force emission depended on the force requirement, such that the force increase occasioned by haloperidol was more prominent in the low-force groups than in the high-force groups (see Figure 1).

Decamethonium did not have a significant effect on peak force of response (see Table 1). Given this drug's known peripheral neuromuscular blocking action (Zaimis, 1953), this lack of a peak force effect is somewhat surprising. However, results for individual subjects (presented later) show that ANOVA statistics derived from the averaging together of subjects with different drug sensitivities can lead to mistaken conclusions in this case.

It is noteworthy that the differences in force emission engendered by both topography and required force did not dramatically deteriorate after drug treatment even though rate declined substantially at higher doses (see Figure 1, middle; note the clear separation in peak force emission among the four groups for each drug). In other words, neither drug at any dose completely abolished the stimulus control exerted by the proprioceptive cues required for emission of forces that the rats had learned were appropriate to the reinforcement contingen-

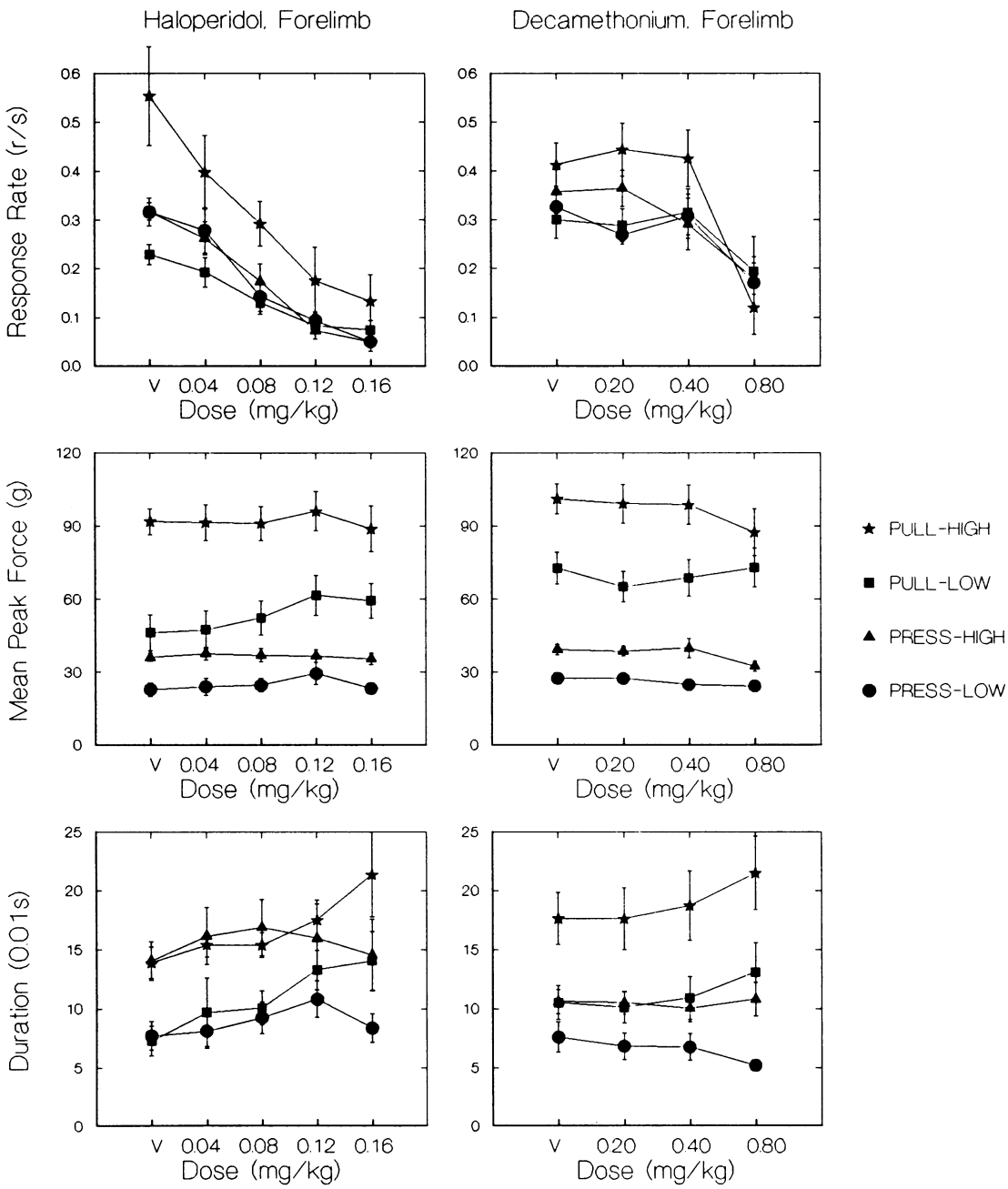

Fig. 1. Effects of the indicated doses of haloperidol and decamethonium on measures of rats' forelimb operant responses. Abbreviations identifying the plot symbols are: press-low: press topography, low-force (8-g) requirement; press-high: press topography, high-force (32-g) requirement; pull-low: pull topography, low-force (8-g) requirement; and pull-high: pull topography, high-force (96-g) requirement. Error brackets indicate ±1 standard error of the mean for a given treatment group.

cies. To bring additional information to bear on this point, the peak force of the very first response of each session was taken as a dependent variable (i.e., one peak force measurement per rat per session). The reason for examining the first response was that it could not possibly be influenced by its consequences in that particular session because no consequences had yet occurred in that session. Thus, the first response of a session allows us to determine whether or not the forces emitted in a session were merely the "tracking" of the required force by using the reinforcer as a discriminative stimulus or whether the force level needed for reinforcement had actually been retained from previous sessions. If the rats were simply tracking, then forces would not be expected to be different on the first response; conversely, if they remembered the force level needed for reinforcement, then forces should be different on the session's first response. Analysis of variance applied to the peak force data for the first response indicated that both topography, $F(1, 28) = 14.605$, $p = .001$, and required force, $F(1, 28) = 5.808$, $p = .023$, effects were present for haloperidol. The same was true for the rats treated with decamethonium: the topography effect was $F(1, 23) = 79.871$, $p < .001$, and the required force effect was $F(1, 23) = 10.027$, $p = .004$. Dose effects on the peak force of the first response were not detected for haloperidol. In contrast, a significant linear trend (the higher the dose, the lower the peak force) was obtained for decamethonium, $F(1, 23) = 15.030$, $p = .001$. This latter result is the first evidence consistent with the idea that decamethonium produces muscle weakness. In none of these ANOVAs on the peak force of the first response were any interaction effects detected.

Forelimb mean duration. As shown in Table 1, required force, under both drug conditions, had a significant effect on forelimb response mean duration, a result consistent with other reports (Fowler, 1987; Notterman & Mintz, 1965). For ballistic responses (i.e., those occurring so rapidly that sensory feedback is too slow to guide the response during its execution), peak force is positively correlated with response duration. As peak force increases so does duration. This is the most parsimonious explanation for the observed effect of required force on mean duration of response.

Topography had a significant effect on forelimb mean duration only in the decamethonium-treated rats. This result is probably related to the fact that the rats in the decamethonium experiment had somewhat less training than the rats in the haloperidol experiment; consequently, response duration had not become fully differentiated. Baseline differences in response duration between the two experiments can be seen for the vehicle condition in the bottom panels in Figure 1. That is, in the haloperidol experiment under the vehicle condition, the two high-force groups (press-high and pull-high) had almost identical, relatively higher mean durations, and the two low-force groups (press-low and pull-low) had nearly identical lower mean durations. But this pattern was not true for the groups in the decamethonium experiment.

Haloperidol elevated response duration (Table 1 and Figure 1). Dose of haloperidol interacted significantly with topography. This interaction arose from the fact that the dose-effect functions for the pull topography displayed a monotonic rise in duration as a function of dose, but dose effects for the press groups exhibited a downturn at higher doses after initial increases at lower doses. In the haloperidol experiment, dose also interacted with required force such that the lower doses had proportionately greater effects on response duration in the low-force groups than in the high-force groups.

Although a main effect for decamethonium dose did not emerge for mean duration (see Table 1), dose interacted significantly with topography. As shown in Figure 1 (lower right), the pull groups displayed a small increase in duration at the highest dose, whereas the press groups remained unaffected or declined at this dose.

Head entry rate. Head entry rate (Figure 2) was not appreciably influenced by either topography or required force, but substantial dose effects were seen for haloperidol and decamethonium (see Table 1 for ANOVA statistics). No interaction effects were detected for head entry rate.

Head entry maximum duration. The maximum head entry duration (Figure 2, lower panels) was significantly affected by haloperidol in a dose-related fashion, but this dependent variable was not influenced by decamethonium. None of the interaction effects was significant (Table 1) for this measure of ad-

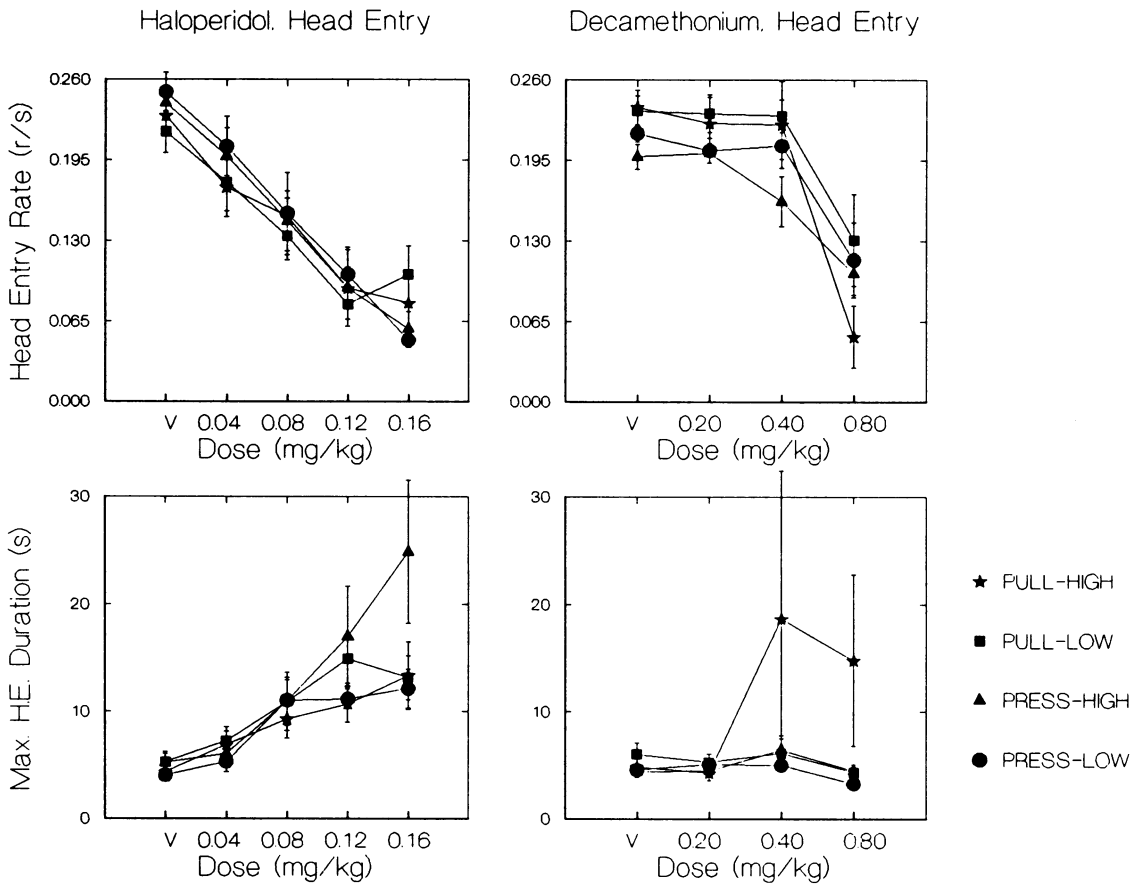

Fig. 2. Effects of dose ranges of haloperidol and decamethonium on two measures of the rats' head entries into the dipper well. Abbreviations and conventions are the same as in Figure 1.

junctive behavior. Of the five dependent variables analyzed, the maximum head entry duration appeared to discriminate most clearly between haloperidol and decamethonium. The two data points with the large standard error brackets shown in the lower right panels of Figure 2 were the result of 1 rat in the pull-high decamethonium group that had a relatively long maximum head entry duration at the two highest doses. This may have been the result of the subject's collapsing in the dipper well because of the muscular weakness produced by decamethonium. Overall, however, decamethonium had little effect on maximum head entry duration even though rate of operant response and head entry rate were reduced markedly at the highest dose. On the other hand, the results for haloperidol appear to be qualitatively different from those for the paralytic agent. For haloperidol, maximum head entry duration increased in a graded fashion as dose increased, and these dose-related changes roughly paralleled the almost linear decline in both operant rate and head entry rate.

Individual Subject Data

Although the foregoing analyses were successful in demonstrating qualitative differences between haloperidol and decamethonium, these analytic methods are open to criticism on the grounds that individual rats with different drug sensitivities were averaged together at each dose, thereby distorting the data. Moreover, one could also contend that statements about qualitative differences between drugs are suspect unless the drugs are somehow equated for their differences in potencies in affecting key components of behavior. For example, one could argue that the response-

rate dose-effect functions for decamethonium are governed by inadequate dose selection, and that decamethonium dose-effect functions for rate could be made to look similar to those for haloperidol by merely choosing doses of decamethonium between 0.40 and 0.80 mg/kg. To address these issues, operant response rate was taken as a behavioral measure for defining equipotent effects of each drug, regardless of dose. Then nonrate measures of behavior (e.g., peak force and duration) were compared at these approximately equivalent doses in terms of response-rate decrement.

Analyses at equivalent rate effects. Individual subject response-rate data were inspected to locate drug-induced rate changes that were as close to a 50% reduction as possible, regardless of actual dose. Because of the relatively abrupt change in rate in going from 0.40 mg/kg to 0.80 mg/kg of decamethonium, in some treatment groups it was not always possible to find rate reductions quite close to 50%; therefore, data were included in this analysis only if the rate reductions were at least 80% of control but not less than 20% of control. The intent was to achieve empirically an approximate dose for each subject that was effective in producing a 50% rate reduction (ED50) (analogous to the ED50 calculated via interpolation based on theoretical assumptions) and then to compare peak force and duration in the same subjects at these same doses. The specific choice of the 80%–20% limits was somewhat arbitrary, but these values ensured that at least a moderate, but not complete, response suppression was exhibited by the individual subject. For the haloperidol experiment, application of the close-to-50% rule resulted in group mean percentage of vehicle control rates: press-low = 40.6%, press-high = 51.0%, pull-low = 45.8%, and pull-high = 39.4%. For decamethonium, these data were press-low = 58.7%, press-high = 60.8%, pull-low = 45.2%, and pull-high = 67.9%. A similar approach was taken with the head entry measures, except that the data for maximum head entry duration were selected on the basis of 50% reduction in head entry rate instead of forelimb operant response rate. The group mean head entry rate percentages of control for haloperidol were press-low = 43.8%, press-high = 41.9%, pull-low = 47.0%, and pull-high = 43.7%; for decamethonium, they were press-low = 54.7%, press-high = 50.5%, pull-low = 45.6%, and pull-high = 35.5%.

Individual subject and group mean data for operant peak force, operant duration, and maximum head entry duration, each expressed as a proportion of control, are shown in Figure 3. In essence, these data are for approximately equally effective doses in producing a moderate response-rate decrement (as described in the preceding paragraph). When the peak force data are viewed in this way (upper panel of Figure 3), differences between haloperidol and decamethonium become quite clear for the press-topography groups; haloperidol increased peak force and decamethonium decreased it. Results for peak force under the pull topography did not yield as clear a separation between the two drugs. With respect to forelimb response duration (middle panel of Figure 3), the clearest difference between haloperidol and decamethonium was again in the press-topography groups, particularly in the low-force rats. Under these conditions, haloperidol tended to increase or not affect response duration, but decamethonium decreased response duration. Of the three dependent variables in Figure 3, maximum head entry duration produced the most consistent differences between the two drugs. Unlike force and duration of response, the head entry maximum duration variable discriminated between haloperidol and decamethonium independently of topography or required force. The possible importance of topography and required force is nevertheless suggested by the fact that the separation between drugs was greatest in the press-low condition. Haloperidol greatly increased (on the average, 300% in the press-low group) the tendency for the rat to remain, at least once per session, in a posture with its head blocking the photobeam. Decamethonium did not produce such an effect. When the data in Figure 3 are taken as a whole, it is clear that the press-low condition yielded the most distinctive contrast between haloperidol and decamethonium.

Representative frequency distributions. The forelimb peak force and duration data (Figure 3) were derived from session averages for individual subjects. It is possible that such averaging may obscure the drug effects that occur at the level of the individual response. For instance, a drug treatment might conceivably

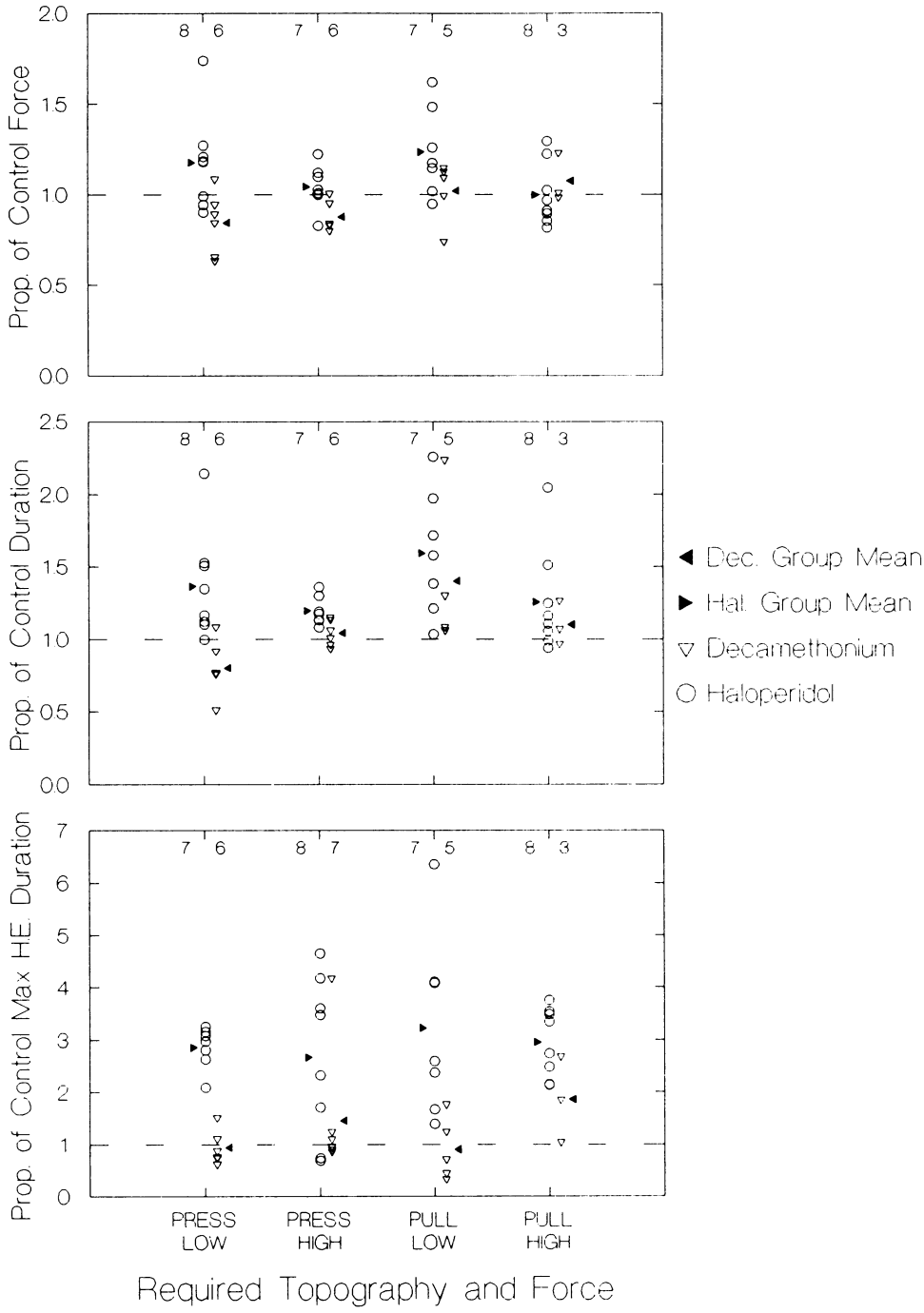

Fig. 3. Forelimb force and duration of response and maximum head entry duration expressed as proportion of vehicle control values. The forelimb data are for rats in each of the four haloperidol groups and the four decamethonium groups that showed a drug-related reduction in forelimb operant response rate between 20% and 80% of control values. Data for maximum head entry duration (bottom panel) are for rats exhibiting a 20% to 80% drug-related reduction in head entry rate. The digits arrayed across the upper border of each set of panels give the number of rats in each drug and condition.

leave a rat's session mean peak force unaffected even while the distribution of peak forces changed appreciably in shape (e.g., from unimodal to bimodal). To investigate this possibility, frequency distributions for vehicle and drug conditions were constructed for 2 rats. One rat was drawn from the press-low haloperidol condition, and 1 was from the press-low decamethonium condition. The 2 rats were the ones closest to having a 50% rate reduction in their respective groups. The actual values were 46.3% and 48.8% of control for haloperidol (Rat 253) and decamethonium (Rat 409), respectively.

Figure 4 compares these 2 rats in terms of frequency distributions and cumulative records of operant responding. The peak force distributions (Figure 4, top row) indicate that haloperidol increased peak force, whereas decamethonium decreased it. Moreover, the largely unimodal nature of both the vehicle and drug distributions shows that the mean is a reasonable, undistorted index of force emission for a given session. Response duration was lengthened by haloperidol and shortened by decamethonium (Figure 4, second row). These distributions are also relatively well represented by the mean. The IRT distributions (Figure 4, third row) simply confirm the fact that the rate under drug conditions for both rats was about 50% of control. The bottom row of Figure 4 provides cumulative records of operant responding in which the vehicle and drug records were plotted (via post hoc computer reconstructions) on the same axes for each rat. The most prominent distinguishing feature of the drug records is that haloperidol produced a long pause late in the session and decamethonium resulted in a pause early in the session.

Figure 5 plots the frequency distributions and cumulative records derived from the head entry data for Rats 253 and 409. It can be seen that the head entry duration distributions under both vehicle and drug conditions appear quite similar for the 2 rats. However, it is also clear that haloperidol increased both the short and the long head entry durations. Thus, in the case of head entry duration, the mean of the distribution was not a useful index of haloperidol's effects even though the mean was a reasonable reflection of decamethonium's lack of effect on this variable. For this reason, mean head entry duration was not included in the group analyses reported in the previous section. Similarly, haloperidol increased the frequency of both short and long interentry intervals (Figure 5, middle row), but decamethonium did not.

For the most part, the cumulative records of head entry events presented in Figure 5 are highly similar to the records for forelimb operant responding shown at the bottom of Figure 4. But one very important exception is obvious: After about two thirds of the session, haloperidol induced Rat 253 almost to cease operant responding, yet during this pause a relatively high rate of head entries was made (compare the haloperidol curves in the lower left of Figures 4 and 5). No indication of this pattern of behavior was seen in Rat 409 (treated with decamethonium).

Cumulative records of operant and head entry responses. The observation that haloperidol may induce a temporal uncoupling of forelimb operant responses and head entry events was unexpected and led immediately to the comparison of additional "dual" cumulative records for the rats in the press-low condition.

Vehicle-derived cumulative records for the 8 press-low rats in the haloperidol experiment are given in Figure 6. When drug free, each rat displayed a relatively tight temporal coupling between forelimb and head entry events. Such outcomes are what one would expect on the basis of the prevailing reinforcement contingencies. The records for forelimb operants and head entry behavior are not completely redundant, however, because rats make superfluous forelimb responses (e.g., Rat 246, Figure 6) as well as unnecessary head entries (e.g., Rat 252, Figure 6). The extra forelimb responses result from the strong tendency (probably unconditioned, see Fowler, 1987) for rats to emit responses in tightly coupled bursts wherein the first transducer strike delivers the reinforcer, but an additional one or two responses follow within 0.1 to 0.4 s before the rat moves to collect a reinforcer. Unnecessary head entries usually occur when the rat hits the silent isometric operandum but does so with a force insufficient to produce reinforcement and attendant auditory cues, and even in the absence of dipper operation the rat completes the sequence of reach-press-release-move-enter dipper well.

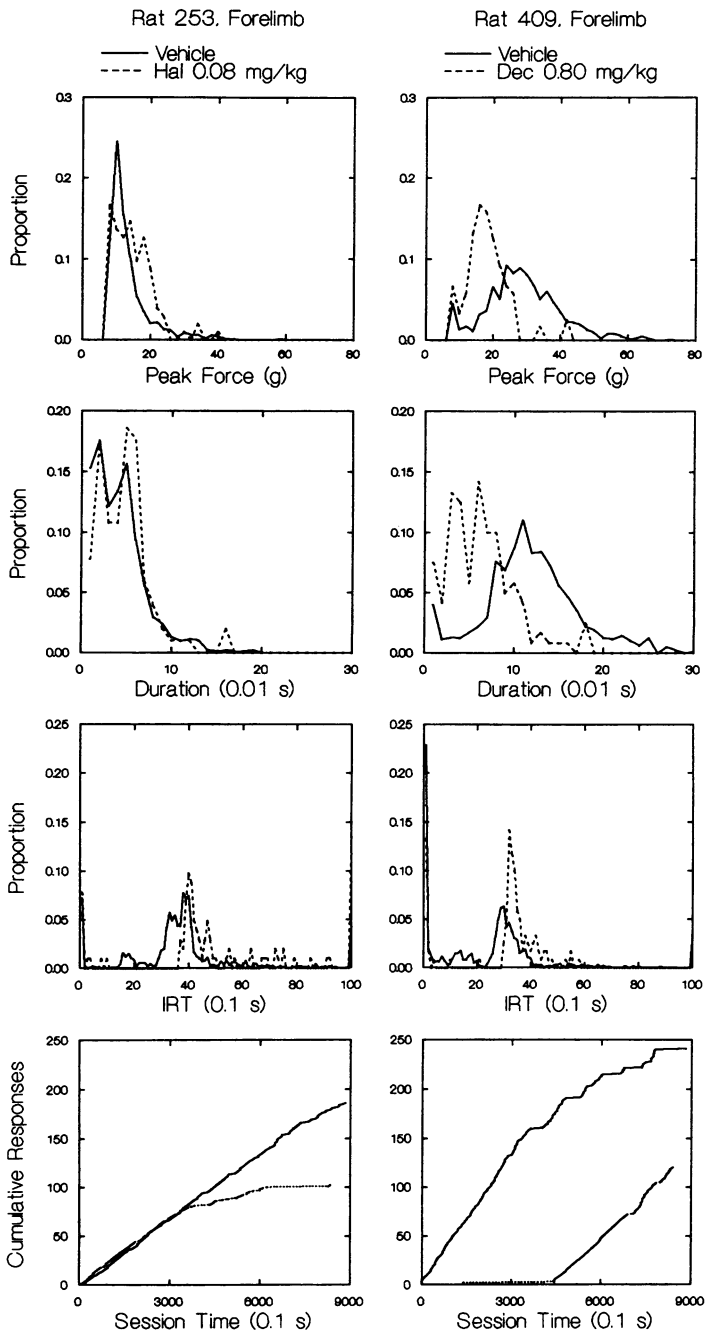

Fig. 4. Forelimb response data for 2 subjects after vehicle or drug treatment. IRT in the third row refers to interresponse time recorded separately from response duration. The computer-generated cumulative records comprising the bottom row were plotted so that the pen was lifted at the last response in a session. Reinforcement delivery is not shown because every response meeting the 8-g force criterion was reinforced.

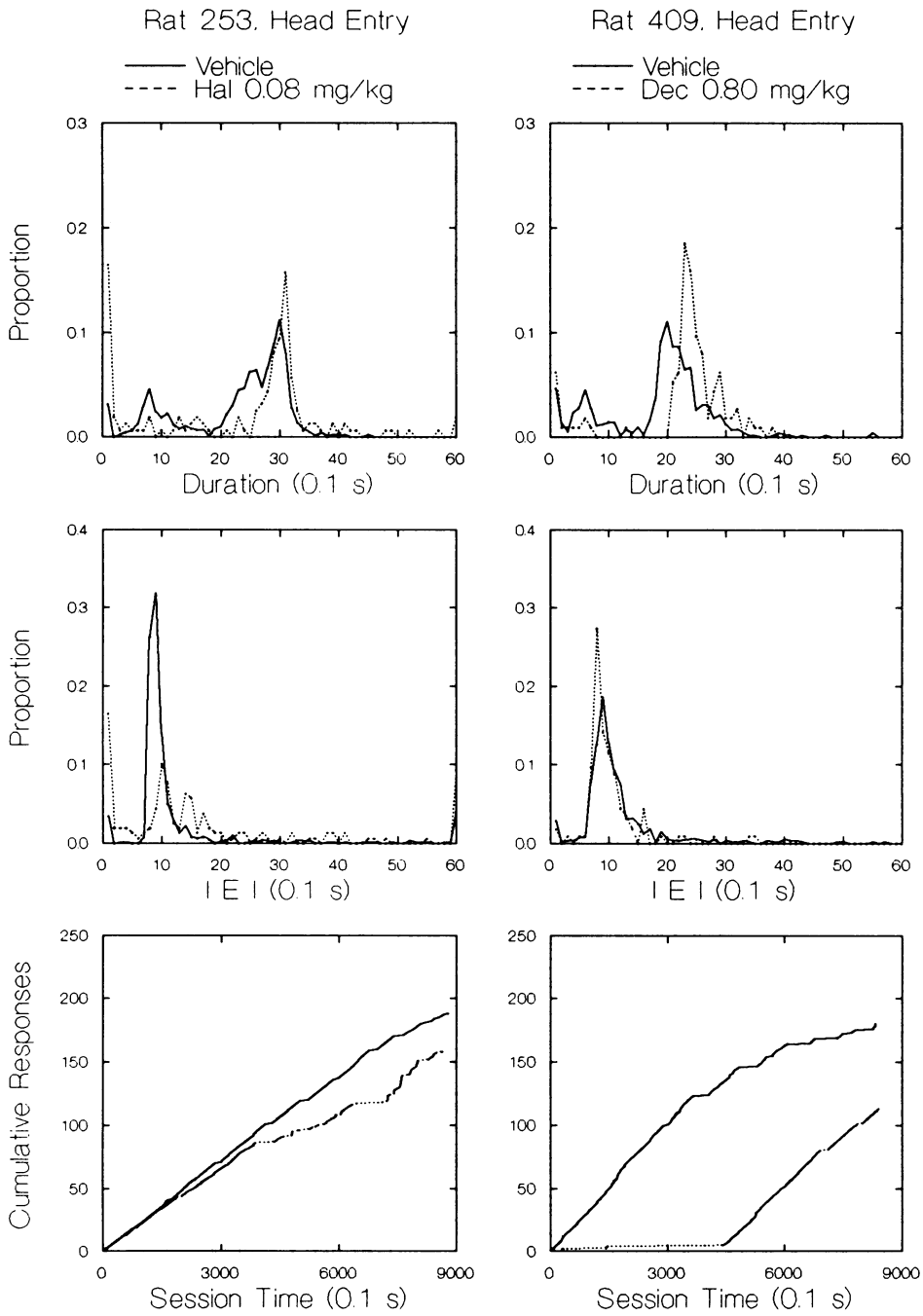

Fig. 5. Head entry data for the same rats and conditions displayed in Figure 4. IEI in the second row refers to interevent interval; this measure was recorded separately from head entry duration.

Figure 7 presents cumulative records for the press-low rats receiving the 0.08 mg/kg dose of haloperidol. All subjects exhibited marked dissociations of operant responses from head entry responses for at least some part of the session. Thus, haloperidol led to bouts of head entry responses without operandum presses and vice versa. Moreover, in some rats (252, 253,

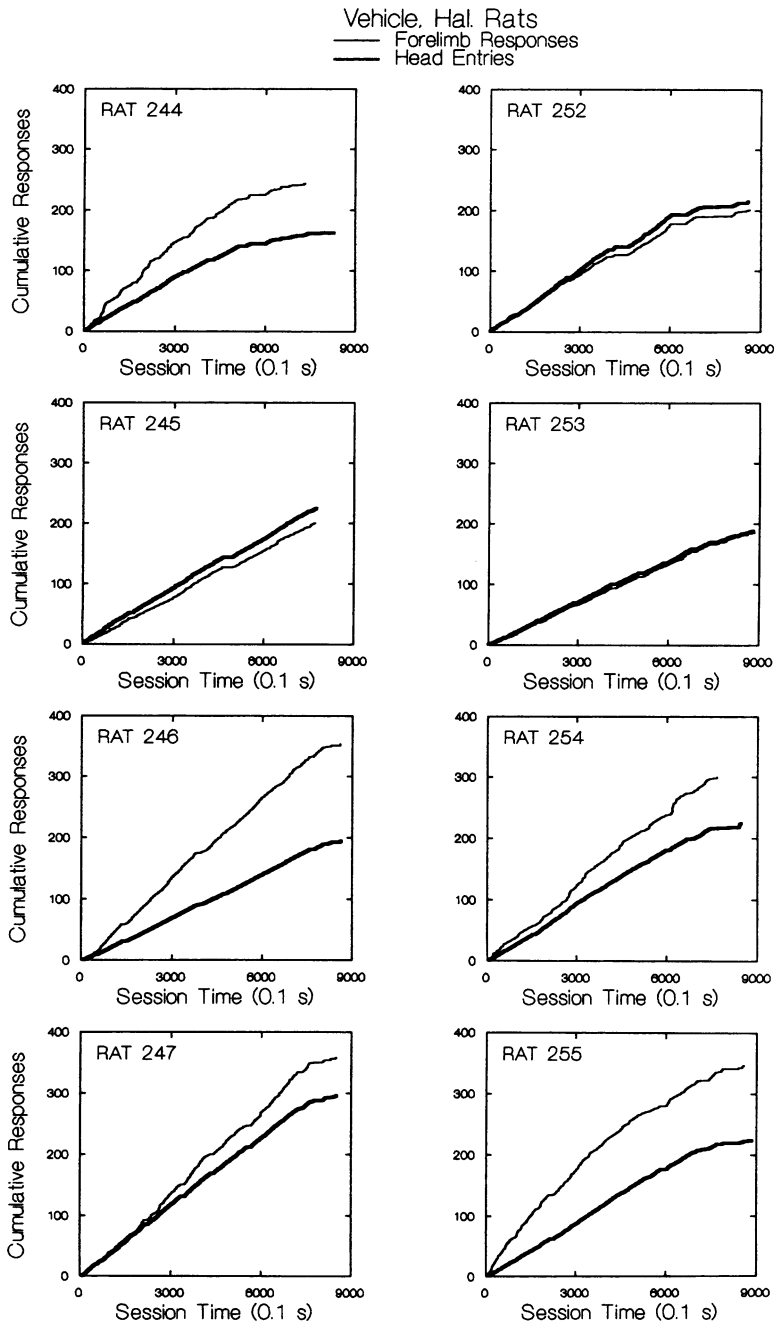

Fig. 6. Illustrating vehicle control performance, these cumulative records of forelimb operants and head entries (thick line) into the reinforcement dipper well are for the rats in the press-low group (see caption for Figure 1) that received haloperidol.

246, 247, and 255), head entries persisted longer in the session than operant responses did.

Figure 8 shows operant and head entry cumulative records for the 8 press-low rats under vehicle conditions in the decamethonium experiment. The strong temporal relationship between operants and head entries in Figure 8 simply confirms what was apparent for the

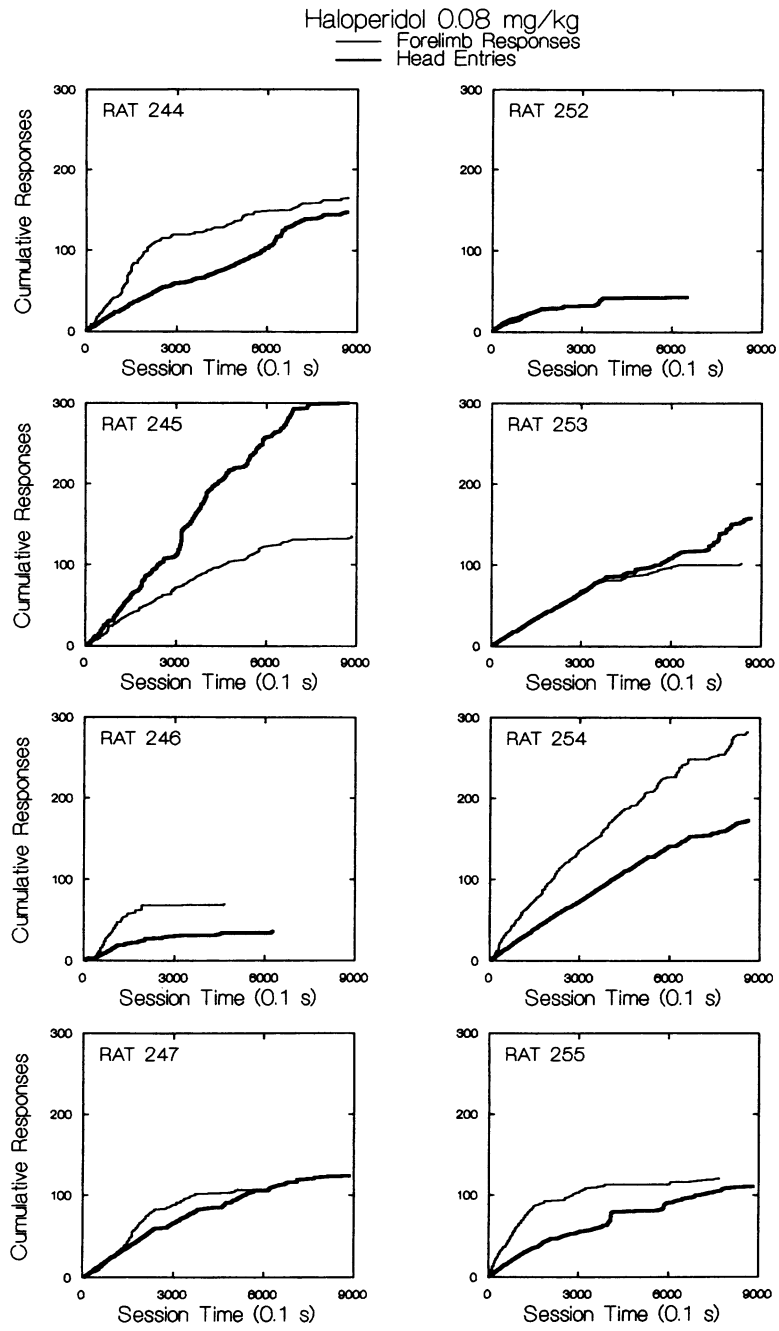

Fig. 7. Cumulative records of forelimb responses and head entry events plotted on the same axes for the 8 rats in the press-low condition responding under the effects of 0.08 mg/kg haloperidol.

haloperidol vehicle-only treatment (Figure 6). However, decamethonium did not appreciably alter the temporal correlation between operant responses and head entries, even though at this dose decamethonium did disrupt normal responding in most subjects (Figure 9).

DISCUSSION

Topography, Required Force, and Stimulus Control

The independent variables, response topography and level of required force, modulated

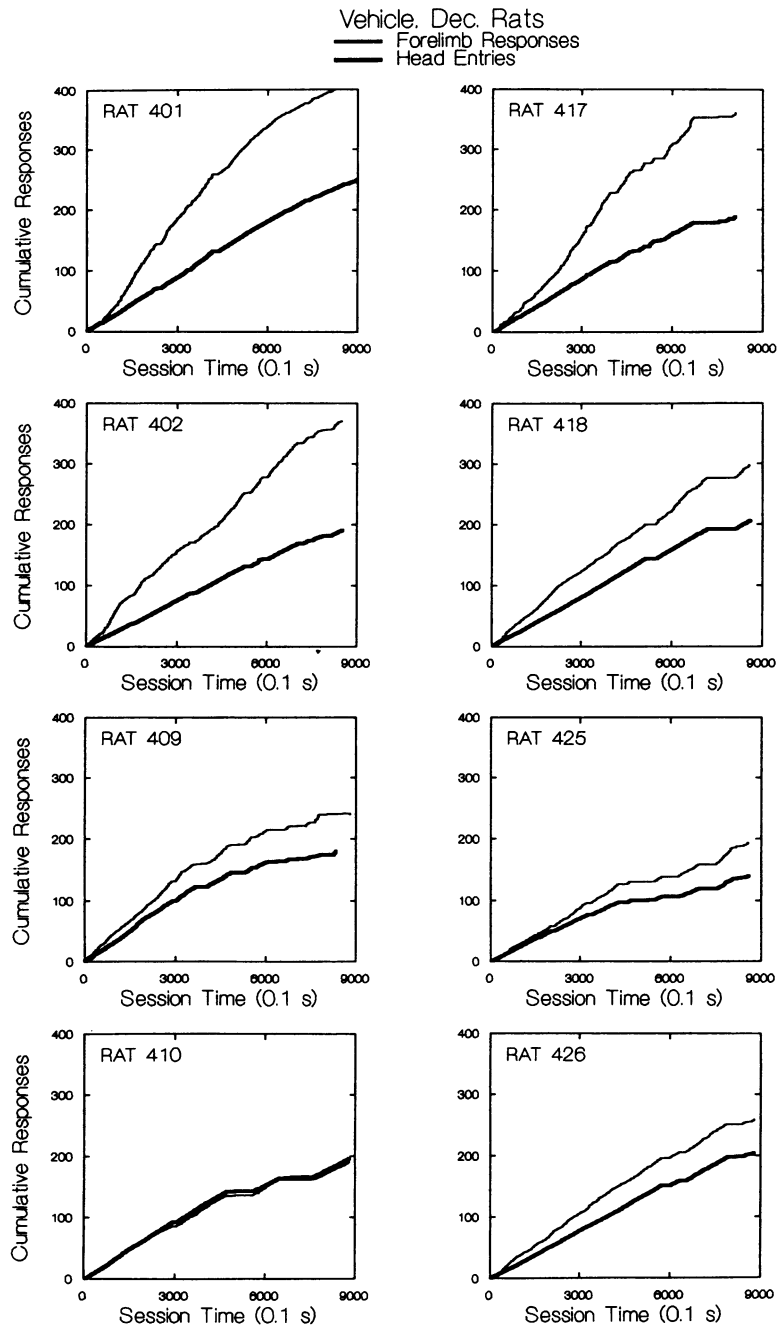

Fig. 8. Vehicle control performances for the decamethonium-treated rats in the press-low condition.

the effects of both drugs on the various measures of operant response. In the combined press topography and low-force condition, separation between haloperidol and decamethonium was clearest for the forelimb peak force and duration variables. The high-force condition may have reduced sensitivity to the different behavioral effects of the two drugs because training on the high-force requirement led to much greater proprioceptive stimulus control than in the low-force conditions. This explanatory hypothesis is analogous to the general principle articulated by Laties (1975): "behavior under strong [exteroceptive] stim-

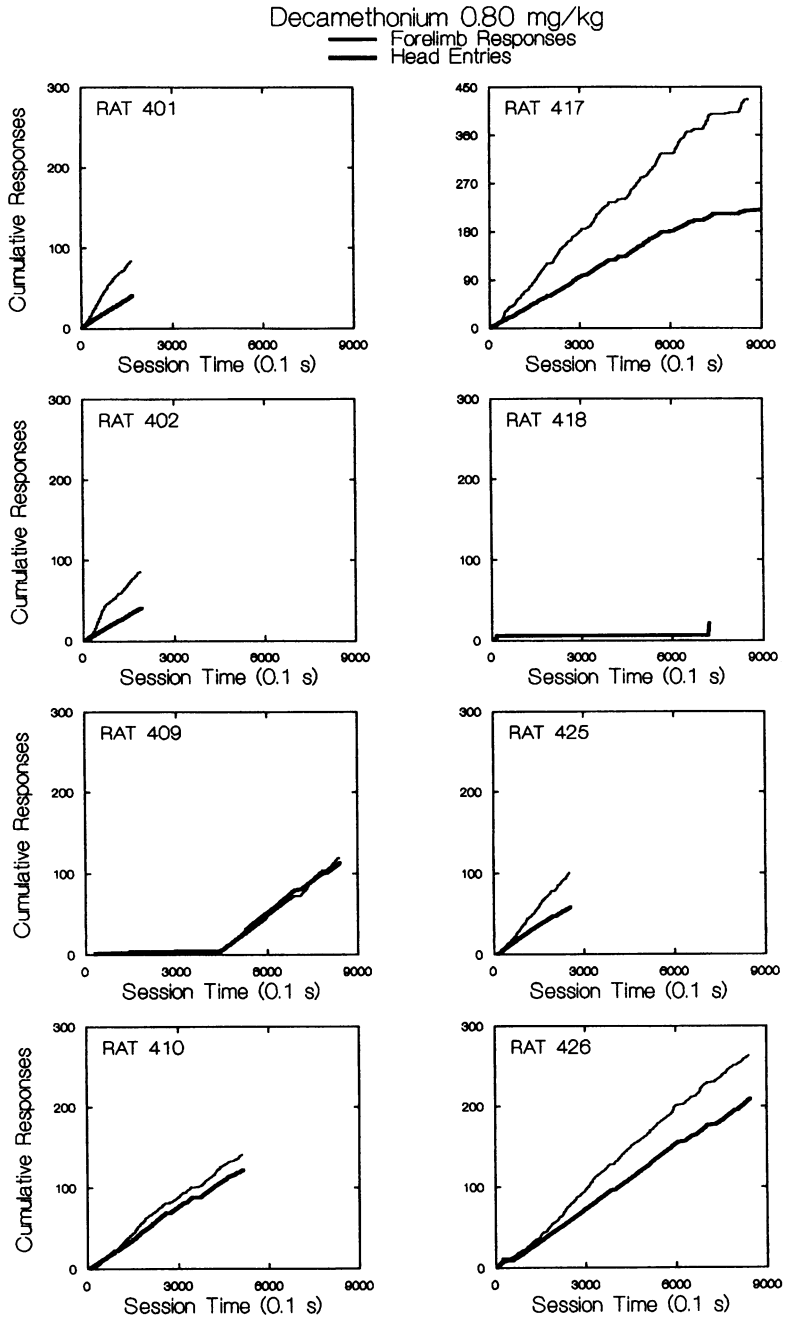

Fig. 9. Cumulative records comparing forelimb and head entry responses for the 8 subjects in the press-low condition after receiving 0.08 mg/kg decamethonium bromide. Note that the ordinate scale for Rat 417 differs from the others. Rat 418 did not emit any forelimb operants under these circumstances.

ulus control is less apt to be readily affected by many drugs" (p. 1880). The current work provides evidence that what is true of strong exteroceptive stimulus control may also be true of powerful proprioceptive stimulus control. An additional possibility is that the high-force conditions produced ceiling effects for haloperidol such that drug-induced increases could

not be observed because baseline force emission may have been near the maximum for a given topography.

The relative insensitivity of peak force of the pull topography to the drugs' effects may be related to the needlessly high force emitted in the pull-low groups. Results here and in previous work (Kirkpatrick & Fowler, 1989) suggest that the pull topography engenders responding with "elicited" or reflexive response components (as defined by Jenkins & Moore, 1973) that make the peak force of the pull response resistant to precise differentiation. By reflexive response components we mean to imply that unconditioned (in the Pavlovian or classical conditioning sense) forelimb contractions may occur in a rat's extended forelimb if the palm is stimulated with a grasping rod of appropriate diameter, especially in the presence of stimuli signaling food. Reflexive responses may be presumed to be under strong stimulus control (whether external or internal) and correspondingly less susceptible to disruption by drug challenges.

Haloperidol and Effortfulness of Response

Consistent with other recent reports (Fowler, Gramling, & Liao, 1986; Fowler & Kirkpatrick, 1989), required force as an independent variable did not appear to be important in determining the effects of haloperidol on response rate. If response rate decrements engendered by haloperidol were due at least in part to alterations in the apparent effortfulness of the responses (Sinnamon, 1982), then dose would be expected to interact with required force in the ANOVA for response rate. But this did not occur. In contrast, dose of decamethonium did interact with required force in the ANOVA on response rate for this drug, a result indicating that the effort concept may be useful in the analysis of some drug-induced disruptions in responding, but not those produced by haloperidol.

Operant Response Duration and Pseudo-Parkinsonism

Like peak force of response, duration of response showed the largest differences between haloperidol and decamethonium in the press-low condition, in which haloperidol increased duration and decamethonium decreased it. Figure 3 shows that for a given rate decrease, response duration was increased proportionately more by haloperidol than by decamethonium in the press-high, pull-low, and pull-high groups. Although this result is consistent with several other studies showing a duration-increasing effect of neuroleptics (Faustman & Fowler, 1981; Faustman, Fowler, & Walker, 1981; Fowler, Gramling, & Liao, 1986; Fowler & Kirkpatrick, 1989; Fowler, LaCerra, & Ettenberg, 1986; Liao & Fowler, 1990), the interaction of haloperidol with topography (see Figure 1, bottom row, and Table 1) deserves additional comment. The greater dose-related increase in response duration in the pull than in the press groups may have been caused by the requirement for greater response complexity in the emission of the pull response. To register a pull response the rat had to (a) extend the forelimb; (b) flex the digits; (c) in coordination with flexure of the biceps, briefly maintain flexure of the digits; and (d) then relax the digits as the biceps retracted the limb back toward the subject. In contrast, the press response requires no digit control to make the response. It has been argued elsewhere that haloperidol-induced slowing of rats' individual motor acts is homologous to Parkinson-like effects of neuroleptics in human patients (Fowler, 1990; Fowler, LaCerra, & Ettenberg, 1986; Fowler, Liao, & Skjoldager, 1990; Liao & Fowler, 1990). If this premise is accepted, then the greater slowing of the pull response compared to the press response can be understood in terms of the greater number of response elements in the pull response; more slowing occurs because a greater number of discrete motor elements are available for expressing the drug effect.

Maximum Head Entry Duration and Catalepsy

Maximum head entry duration discriminated well between haloperidol and decamethonium independently of topography or required force. The fact that haloperidol lengthened maximum head entry duration is consistent with the idea that D2 dopamine receptor blockade produces pseudo-Parkinsonism in rats (Fowler, 1990; Fowler & Kirkpatrick, 1989; Fowler, LaCerra, & Ettenberg, 1986; Fowler et al., 1990), even at supposedly subcataleptic doses. In rats, catalepsy is a marked tendency to remain for several minutes in a posture that would ordinarily endure only a few seconds in an undrugged rat. Such effects are clearly observable at haloperidol doses

above 0.5 mg/kg (i.p.). Previous work has shown that haloperidol-induced catalepsy is characterized by an intensification of static postural support mechanisms that interfere with movement (e.g., De Ryck, Schallert, & Teitelbaum, 1980; Wolgin, 1985). It is hypothesized here that the few, relatively long head entry durations induced by low doses of haloperidol represent the first manifestations of catalepsy (i.e., the rat occasionally remains motionless with its head blocking the photobeam). The fact that maximum head entry duration increased monotonically as a function of dose is in accord with the idea that the observed effects are mild catalepsy, because the intensity of catalepsy is known to increase with dose. This hypothesis regarding maximum head entry duration is also consistent with the idea that neuroleptics interfere with response initiation (e.g., Posluns, 1962; Skjoldager & Fowler, 1988). This follows from the fact that in an undrugged rat, termination of a head entry is closely followed by an operant response; therefore, the drugged rat's failure to leave the dipper well is tantamount to retardation in the initiation of the next operant-consummatory sequence.

Dissociative Effects of Haloperidol

Although pseudo-Parkinsonism appears to account for the observed response slowing produced by haloperidol, the relevance of this analogy to the altered patterns of behavior depicted in Figure 7 is not so obvious. The temporal uncoupling of forelimb operants and head entries suggests an explanation in terms of dissociative processes (i.e., the breakdown of an association, possibly between responses). Several studies (reviewed by Beninger, 1989) have implicated associative processes in the behavioral decrements produced by neuroleptics. Moreover, neuroleptics' well-known disruption of conditioned active avoidance can be interpreted as a breakdown in stimulus–response association because the conditioned stimulus fails to elicit the appropriate response. Recently, Cutmore and Beninger (1990) have presented data suggesting that neuroleptics impair performance on learning tasks in schizophrenic patients. Even in Parkinson's disease, a naturally occurring hypodopaminergia, evidence has favored an associative ("cognitive") deficit (e.g., Sager, Sullivan, Gabrieli, Corkin, & Growdon, 1988). All of this evidence supports the hypothesis that neuroleptics that block dopamine receptors possess dissociative as well as motor effects. Whether the motor effects themselves produce the temporal dissociation between forelimb and head entry events observed here for the rat or, alternatively, whether the motor and dissociative effects are different but parallel pharmacological effects cannot be determined from the data presented.

Consideration of Pharmacokinetic Factors

Certain patterns of responding seen in the cumulative records (Figures 7 and 9) raise the possibility that pharmacokinetic factors may be important in within-session rate changes observed in some instances. For example, the progressive decline in rate after haloperidol treatment (Figure 7) or the abrupt cessation of or resumption of responding seen after decamethonium treatment (Figure 9) may conceivably be the result of changing brain or blood levels of the drugs. Because the time between injection and behavioral observation was not studied systematically, the influence of pharmacokinetic factors cannot be inferred from the data reported here. However, results in the literature provide relevant information on this issue. Detailed kinetic data on levels of haloperidol in the rat brain (Ohman, Larsson, Nilsson, Engel, & Carlsson, 1977) indicate that, with the 45-min presession injection time and the intraperitoneal route of injection, drug concentration in the brain was either steady or decreased slightly during the 15-min operant session. On the other hand, the cumulative records for decamethonium, a drug that has both a relatively fast onset of action and a rapid elimination (Zaimis, 1953), may have been influenced by changing blood levels during the operant session. Although kinetic factors may have influenced the temporal patterns of responding seen for decamethonium, such factors cannot account for the temporal correlation between forelimb and head entry rate because these were occurring within seconds of one another. Likewise, for the results obtained under conditions of 50% rate reduction (Figure 3), any kinetic factors were presumably controlled for by selecting data on the basis of approximately equal rate reductions produced by decamethonium.

Haloperidol Does Not Induce Muscle Weakness

From a strictly empirical perspective, the current data show that under favorable ob-

serving conditions (low-force requirement and press topography), haloperidol and decamethonium yielded qualitatively different behavioral profiles. Haloperidol increased peak force and duration of operant response, increased maximum head entry duration, and temporally uncoupled forelimb and head entry behavior. Decamethonium decreased force and duration of operant response, did not appreciably affect maximum head entry duration, and did not influence the normal temporal coupling of forelimb and head entry responses. By way of theoretical summary, the haloperidol profile is similar to pseudo-Parkinsonism, and the decamethonium profile is consistent with peripheral muscle weakness.

Epilogue in Support of the Cumulative Record

A final methodological comment seems warranted. In this era of computer-based recording, many investigators have neglected the cumulative record. The current results show how valuable cumulative records can be in presenting information that is difficult to appreciate in any other format. The temporal dissociation of forelimb operants and head entries engendered by haloperidol would have been overlooked without a propitious combination of computer and traditional methods of constructing cumulative records.

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